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Physiological Basis of Fescue Toxicosis

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Abstract

Tall fescue toxicosis continues to be a major syndrome in temperate climates of the world in terms of economic loss to animal producers. Studies with forage-fed animals over the past three decades have provided insight concerning the pathophysiological effects of the alkaloids present in tall fescue [*Lolium arundinaceum* (Schreb.) Darbysh.] infected with the fungal endophyte *Neotyphodium coenophialum* (Morgan-Jones and Gams) Glenn, Bacon, and Hanlin. To provide the reader a general understanding of the overall problem, we present a detailed discussion of the clinical signs of fescue toxicosis, the proposed toxicants, and projected solutions to this costly disease condition of ungulates. We also explore the physiological mechanisms proposed to be involved in the expression of the syndrome. Finally, we offer our suggestions for future research efforts in this arena and the potential impact of these approaches.

Tall fescue is an economically important cool-season perennial forage grass covering about 15 million ha in the United States alone (Buckner et al., 1979) and many more in continents outside North America (see Chapter 3, Hannaway et al., 2009, this publication). The vast majority of the tall fescue in the United States is grown within the transition zone of the eastern and central part of the country. With the development of novel nontoxic endophytes, tall fescue is again becoming increasingly popular for pastures in New Zealand and Australia. The wide distribution of tall fescue has been attributed to its symbiotic relationship (see Chapter 14, Christensen and Voisey, 2009, this publication) with the endophytic fungus *Neotyphodium coenophialum* (Glenn et al., 1996). Although beneficial to the plant, the presence of the wild-type endophyte (i.e., toxic form) in tall fescue forage consumed by ungulates (e.g., cattle, horses, sheep) has induced a toxicity syndrome known collectively as *tall fescue toxicosis* (often shortened to *fescue toxicosis*) considered to be the major grass-induced toxicosis in the United States (Cheeke, 1995).

Fescue foot, a malady of fescue toxicosis, is characterized by the following signs or combinations of them: tenderness and/or swelling around the fetlock and hoof region, lameness, dry gangrene (tissue necrosis) of tips of ears and tails and surrounding tissues, and loss of tail switch (Cunningham, 1948). In the most advanced cases, hooves of affected animals may slough off. Such clinical signs are manifestations of the effects of ergot alkaloids on blood vessels, which result in damage to vessel-lining cells, enhanced blood clotting, narrowing (vasoconstriction) of the vessel lumens (Tor-Agbidye et al., 2001), and ultimately lack of blood flow (Strickland et al., 1993; Oliver, 1997, 2005).

Summer slump and *fat necrosis*, terms less used today than a few years ago, are components of the overall fescue toxicosis syndrome and are characterized by reduced body weight (BW) gain during summer and necrotic fat formation, respectively (Strickland et al., 1993). There are no external signs of fat necrosis apart from poor thrift in cases where necrotic fat is constricting internal organs. In addition to these signs, the majority of afflicted animals express the following conditions in varying degrees: poor growth rate, rough haircoat, elevated body temperature, increased respiration rate, excessive salivation, and reduced milk production by cows or agalactia (cessation of milk production), particularly in horses. Behaviorally, affected animals often seek shade, form wallows around water troughs and in shaded areas, and spend less time grazing than their unaffected counterparts (Schmidt and Osborn, 1993; Strickland et al., 1993; Oliver, 1997, 2005).

Perennial ryegrass (*Lolium perenne* L.) commonly is infected with a similar endophyte (*N. lolii* Latch, M.J. Christensen & Samuels) that likewise produces ergot alkaloids. Consumption of infected ryegrass results in a syndrome that is similar to fescue toxicosis, but sometimes milder. Toxicosis signs derived from ergot alkaloids often are included incorrectly in the *ryegrass staggers* syndrome. In contrast, ryegrass staggers is caused by a tremorgenic mycotoxin, lolitrem B, which is produced also by *N. lolii*. Although ryegrass staggers is not caused by ergot alkaloids, both staggers and tall fescue toxicosis can be induced by the same ryegrass–endophyte association (Fletcher and Easton, 1997; Fletcher et al., 1999; Fletcher, 2005).

Before association of *N. coenophialum* with fescue toxicosis, attempts to identify the agent(s) responsible for the intoxication led to identification of several classes of candidate compounds (Yates et al., 1989). These included halostachine, perloline, β-carboline alkaloids, loline alkaloids (i.e., saturated pyrrolizidine alkaloids), and several ergot alkaloid classes (e.g., clavines, lysergic acid derivatives, ergopeptines). Although candidates have been proposed as possible toxicants, the primary agent or set of agents has not been elucidated completely. Relatively recent research findings generally favor the ergot alkaloids as the primary agents of intoxication, with ergovaline and lysergic acid being top candidates (see Chapter 13, Bush and Fannin, 2009, this publication). Additional research is required to confirm which of these or other compounds are of primary concern for each of the affected physiological systems in grazing animals.

A complete evaluation of these compounds is beyond the scope of this chapter. The reader is directed to the review by Strickland et al. (1993) for information concerning halostachine, perloline, β-carboline, and loline alkaloids, as these have recently become of little concern in relation to fescue toxicosis. The remainder of this discussion will focus on the potential involvement of ergot alkaloids in the physiological dysfunctions associated with fescue toxicosis. It is intended to stimulate discussion of future research directions to clarify our knowledge of the causative agents and physiological mechanisms responsible for the fescue toxicosis syndrome. Broadening our insight into the physiological basis of this costly syndrome will improve our design of management protocols for alleviating toxicosis from tall fescue.

Toxicokinetics of the Ergot Alkaloids

The toxicokinetic aspects of tall fescue toxicants remain ill-defined. However, the pharmacokinetics of the drug bromocryptine (a synthetic ergot alkaloid) have been studied in a number of species (see review by Oliver, 1997) and indicate significant first-pass biotransformation of this alkaloid in the liver. Whether naturally occurring ergot alkaloids are similarly metabolized in ungulates remains to be determined. Naturally occurring ergot alkaloids have been detected in serum (Savary et al., 1990; Bony et al., 2001), urine and bile (Stuedemann et al., 1998; Schultz et al., 2006), ruminal and abomasal fluids (Westendorf et al., 1993; Craig et al., 1994), milk (Durix et al., 1999), and feces (Westendorf et al., 1993; Schultz et al., 2006) of sheep, cattle, and/or horses (see Chapters 16 [Waller, 2009] and 17 [Cross, 2009], this publication). When administered to ruminants, 50 to 60% of ergot and loline alkaloids were recovered in abomasal contents, while very little reached the ileum and only 5% were recovered in fecal collections, indicating extensive absorption from the gastrointestinal system (Piper and Moubarak, 1992; Westendorf et al., 1993). Stuedemann et al. (1998) provided data that supported results of Piper and Moubarak (1992) and Westendorf et al. (1993) concerning absorption of the alkaloids by the gastrointestinal system of ruminants. They reported that as much as 96% of the ergopeptine alkaloids (i.e., complex ergot alkaloids such as ergovaline and ergotamine) were excreted in the urine of cattle grazing endophyte infected (E+) pasture. Very little of the alkaloids consumed by these same animals was detected in the bile. This compared well with findings by Westendorf et al. (1993) that fecal ergot alkaloid recovery was only 6 to 7% when sheep received an E+ tall fescue seed diet for about 6 d (Westendorf et al., 1993). These findings would indicate that, in ruminants, gastrointestinal absorption of ergot alkaloids is in the range of 93 to 96% of the amount consumed. However, although both urine and feces were reported by Schultz et al. (2006) to be routes of ergot alkaloid excretion in horses, the amount of ergovaline, as a percentage of intake excreted in the feces, was substantially higher than that found by Westendorf et al. (1993) and Stuedemann et al. (1998) for sheep and cattle, respectively. In fact, the feces of exposed horses contained 35 to 40% of the total ergovaline consumed, indicating the feces were an important route of excretion for intact ergovaline in the horse. Furthermore, contrary to findings of Stuedemann et al. (1998) and Westendorf et al. (1993) for ruminants, ergovaline was not detected in the urine of geldings consuming the E+ tall fescue seed diet (Schultz et al., 2006). This would indicate that the remaining 60 to 65% of the ergovaline apparently were retained or metabolized to another form, perhaps lysergic acid.

Until relatively recently, it had been assumed that ergovaline, an ergopeptine, was the most important ergot alkaloid produced by the wild-type *N. coenophialum* endophyte in connection with the fescue toxicosis syndrome. However, recent gastrointestinal absorption research has suggested lysergic acid may play a more important role in fescue toxicosis than originally thought (Hill, 2004). Transport of ergot alkaloids across ruminal and omasal tissues was evaluated using parabiotic chambers. Lysergic acid was the only ergot alkaloid reported to be transported across these tissues, as measured by enzyme linked immunosorbent assay (ELISA) (Hill and Agee, 1994). From this observation, it was concluded that lysergic acid, not ergovaline, was the primary toxin causing fescue toxicosis. However, in a previous study (Hill et al., 2001), the authors reported that other ergot alkaloids (ergonovine, ergotamine, ergocryptine) were in fact transported across ruminal and omasal tissues, although not to the same extent as lysergic acid and lysergol. For both experiments, the ELISA method of Hill and Agee (1994), which is a nonspecific assay for total ergot alkaloid analysis, was used for quantification of transport. Findings by Schultz et al. (2006) suggested that lysergic acid was excreted by the horse in the feces in greater quantity than consumed (about 133% of total lysergic acid consumed), and more than 200% of the total lysergic acid intake was accounted for in the urine. These data were confirmed by high performance liquid chromatography (HPLC) (Craig et al., 1994; Jaussaud et al., 1998); thus, they were specific for the ergovaline discussed earlier and the lysergic acid discussed here. As mentioned, geldings in this study receiving the E+ tall fescue seed diet apparently retained 60 to 65% of the total ergovaline consumed. Currently, the site of transport of the ergot alkaloids in hindgut fermenters (i.e., equines) has yet to be determined. This led Schultz et al. (2006) to speculate that metabolism of ergovaline (or other ergot alkaloids not measured) to lysergic acid in the stomach, small intestine, hindgut, or the hepatic tissues may explain the excess levels of lysergic acid excreted by these animals in relation to intake.

The apparent differences in the metabolism and/or elimination of the ergot alkaloids discussed in the literature (Westendorf et al., 1993; Stuedemann et al., 1998; Hill et al., 2001; Schultz et al., 2006) may be due to a number of potential physiological differences among ungulates, including but not limited to diet selection and intakes, rate of digesta flow, hindgut versus foregut fermentation, affinity and capacity of absorption, excretory mechanisms, and hepatic and gastrointestinal tract epithelial metabolism. There is much research that still needs to be conducted concerning the effects of species, age, gender, and nutritional and physiological states on ergot alkaloid metabolism and elimination before a clear picture of the complete implications of, and solutions to, the intoxication can be realized fully.

Analytical Methods

One of the reasons that ergot alkaloid metabolism in ungulates has not been defined adequately is the lack of a robust and logistically favorable analytical method for determination of all the alkaloids and their metabolites. Currently, the primary methods for quantification of ergot alkaloids include HPLC (Craig et al., 1994; Jaussaud et al., 1998), ELISA (Hill and Agee, 1994), and high performance liquid chromatography–mass spectrometry (HPLC-MS) (Yates et al., 1985;

Lehner et al., 2004). The ELISA method is rapid but not specific for a given ergot alkaloid. In fact, Hill and Agee's (1994) data would support a bias toward simpler ergots, such as lysergic acid, over the more complex forms like ergovaline. As a result, use of the ELISA method is restricted primarily to total ergot alkaloid level determinations and thus is of limited use for aiding in the determination of mechanisms associated with alkaloid absorption and metabolism. However, this assay has been functioning well, based on all reports so far, as a diagnostic test for ergot alkaloid exposure.

The HPLC methods of Craig et al. (1994) and Jaussaud et al. (1998) are specific but suffer from a need for pure standards of each alkaloid of interest to establish identities of alkaloids by retention time. As such, these methods are limited in their use for discovery research concerning alkaloid metabolites. These methods, however, are excellent for determining profiles of known alkaloids in a number of matrices (e.g., animal serum, feces, and urine). The HPLC-MS methods (Yates et al., 1985; Lehner et al., 2004) offer the greatest opportunity for discovery work involving the full array of ergot alkaloids and their metabolites. As with HPLC methods that use fluorescence detection, analysis by HPLC-MS provides identification and quantification of ergot alkaloids with known chemical structures. However, a third dimension of information in the form of a mass spectrum also is acquired for each component in the sample mixture. Molecular mass can be derived from this MS data for confirmation of known alkaloids separated by HPLC. For novel ergot alkaloids and any corresponding metabolites as a result of biotransformation, a single HPLC-MS analysis can provide retention times, molecular mass, and empirical formulas from isotopic distribution information. Furthermore, tandem mass spectrometry (MS/MS), in which a molecular ion can be isolated and fragmented within the mass analyzer, can provide clues for elucidation of chemical structure of unknown ergot alkaloids and corresponding metabolites. The growing availability of HPLC-MS/MS will provide us with the ability to examine other ergot alkaloids and metabolites, allowing for a better understanding of toxicant fate in ungulates.

If our knowledge of the mechanisms for metabolism and the absorption/excretory routes for the ergot alkaloids is limited in ungulates, our knowledge of the kinetic rates of clearing is even more restricted. Little research has been conducted in ungulates, largely due to the lack of sufficient and/or affordably priced quantities of pure ergot alkaloids of interest available for large animal studies. Jaussaud et al. (1998) reported that the plasma clearance of ergovaline administered via an intravenous injection (17 μg/kg BW) to sheep was 0.02 L/min/kg BW. Similarly, Bony et al. (2001) injected geldings with 15 μg ergovaline/kg BW and observed a plasma clearance rate of 0.02 L/min/kg BW. However, because only plasma ergovaline concentrations were evaluated in these studies, it remains unclear as to whether ergovaline was sequestered in tissues, metabolized (e.g., to lysergic acid), or actually eliminated from the body. Fully understanding the metabolism, distribution, and clearance of these alkaloids in ungulates would facilitate the design of better protocols for improving animal tolerance to E+ tall fescue.

Nutrition and Growth

Decreased weight gain and feed intake are common intoxication responses by most species (e.g., cattle, rats, rabbits, and horses) to consuming E+ tall fescue

(Schmidt et al., 1982; Hoveland et al., 1983; Daniels et al., 1984; Neal and Schmidt, 1985; Bond and Bolt, 1986; Redmond et al., 1991; Aiken et al., 1993). Patterson et al. (1995) concluded from a review of grazing experiments with E+ tall fescue that steer average daily gain (ADG) ranged from 0.20 to 0.62 kg/d, substantially less than for endophyte free (E–) or novel nontoxic endophyte tall fescues (Parish et al., 2003). Aiken et al. (1993) reported that ADG of yearling geldings was less ($P <$ 0.01) on high E+ tall fescue than on forage with low levels of infestation. However, gelding growth in wither heights was similar ($P > 0.10$) on both fescue regimes. Feed intake and growth in sheep did not appear to be as affected as for other species (Porter and Thompson, 1992). These data indicate potential species differences in susceptibility, but the exact cause of these differences remains to be determined and may provide clues to a potential solution.

General growth effects probably are due to the reduced feed intake and/or reported digestibility effects of E+ tall fescue in sheep, cattle, and horses (Hannah et al., 1990; Fiorito et al., 1991; Redmond et al., 1991; McCann et al., 1992), both of which would decrease available nutrients for growth and maintenance. Causes of reduced feed intake still remain elusive; potential effects of endophyte-produced tall fescue toxicants on feeding and satiety centers, gastrointestinal tract motility, blood flow patterns, heat stress, and/or a sensation of sickness are all possibilities. Recent food preference studies with rabbits (Panaccione et al., 2006) using genetically modified endophytes (*Neotyphodium* spp. related to wild-type in tall fescue) in perennial ryegrass demonstrated that rabbits preferred novel over E– perennial ryegrass, neither of which contained ergot alkaloids. The preference of rabbits for E– perennial ryegrass with clavine alkaloids (precursors to ergovaline) was equivalent to that for E– perennial ryegrass. However, E+ ryegrass with ergovaline (an ergopeptine) had a negative effect on intake levels in subsequent meals. This provides the first evidence that ergopeptines, not other potential toxicants in E+ tall fescue, may be linked to restricted feed intakes in grazing animals.

Controlled-intake digestibility studies have provided clues to nutrients most affected by the consumption of E+ tall fescue without the confounding influence of feed intake differences reported above. Hannah et al. (1990) reported reduced ruminal and total tract organic matter, neutral detergent fiber (NDF), and cellulose digestibility in sheep consuming diets containing E+ tall fescue seed with 3 mg/kg of ergovaline. In a similar study, Fiorito et al. (1991) reported a study in rumen-cannulated sheep in which dry matter consumption was forced via the cannula to balance intakes between E+ and E– tall fescue. They reported that total tract dry matter, NDF, and acid detergent fiber (ADF) digestibilities were depressed by the presence of E+ tall fescue hay in the diet. Likewise, Westendorf et al. (1993) reported similar findings with total tract dry matter, ADF, NDF, and crude protein (CP) digestibilities, which were suppressed in sheep by inclusion of E+ tall fescue in the diet. In an attempt to define the mechanism of these reported digestibility effects in ungulates, Harmon et al. (1991) conducted portal and hepatic nutrient flux experiments in limit-fed steers consuming E+ or E– tall fescue hay. They reported no differences in dry matter or N digestibilities between tall fescue treatments and ruminal total volatile fatty acid concentrations, and molar proportions were not affected. Net portal flux of acetate was increased, but no other effects on nutrient flux were noted. The one minor change in acetate taken by itself did not support major effects of E+ tall fescue on ruminal metabolism of nutrients.

Results of Harmon et al. (1991) are in contrast to those reported by Hannah et al. (1990), Fiorito et al. (1991), and Westendorf et al. (1993) for sheep fed either seed or hay diets. There are several reasons why the differences may have occurred, such as differing levels of ergot alkaloids, quality of the diet, species differences, and ruminal microbial populations. In support of diet quality as a potential factor, digestibility results with horses have been reported to change in relation to the type of diet fed. Redmond et al. (1991) and McCann et al. (1992) reported lower digestibilities for E+ tall fescue hay fed to mature geldings and yearling horses, respectively. In contrast, McCann et al. (1993), Pendergraft and Arns (1993), and Schultz et al. (2006) reported no effect of E+ tall fescue, either as hay or seed, but these studies included grain in the total diet. All these metabolism studies, when considered together, indicate that nutritional plane may affect the efficiency of digestion.

Reproduction

Reproductive effects have been noted in several species consuming E+ tall fescue, including mice, rabbits, horses, sheep, and cattle (Daniels et al., 1984; Boling, 1985; Zavos et al., 1987; Bond et al., 1988; Monroe et al., 1988; Porter and Thompson, 1992; Jones et al., 2003; Schuenemann et al., 2005). Ruminants typically have reduced conception rates and, thus, reduced reproductive efficiency. However, monogastrics and hindgut fermenters generally appear to be more susceptible to serious manifestations (e.g., dystocia, abortion) of reproductive maladies than ruminants (Strickland et al., 1993). At present, the cause of this apparent differential effect is not entirely clear. As with digestibilities and intakes, a number of physiological differences among species could account for the differential effect, including blood flow and placental barriers, heterogeneity of receptors and transport systems, microbial and/or gastrointestinal and hepatic biotransformation of reproductive toxicants (not as of yet identified but suspected to be ergot alkaloids), presumably produced by E+ tall fescue.

By far, the animal most affected to date by E+ tall fescue consumption is the late-term mare. Hoveland (1993) estimated that nearly 680,000 horses were kept on tall fescue pastures in the United States. For many years managers and veterinarians reported reproductive problems in mares consuming tall fescue. However, it was not until 1988 (Monroe et al., 1988) that a conclusive link between E+ tall fescue and the reproductive problems was established. Equine reproductive fescue toxicosis is a particularly severe reproductive consequence to pregnant mares consuming wild-type E+ tall fescue, especially late in gestation. They exhibit prolonged gestation, dystocia, retained and thickened placentas, poor milk production, or agalactia (Monroe et al., 1988). They often deliver large, emaciated, and immature-appearing foals, with loss of both the foal and mare common (Cross et al., 1995). Ireland et al. (1991) reported that the administration of bromocryptine (a synthetic ergopeptine) to pregnant pony mares induced a reproductive syndrome that was similar to that observed with E+ tall fescue. These studies, taken together with the identification of ergot alkaloids (especially the presence of ergopeptines like ergovaline) in E+ tall fescue (Lyons et al., 1986), provided strong evidence that ergot alkaloids were the causative agents of the equine reproductive fescue toxicosis. Attempts to curtail toxicity using a biogenic amine receptor antagonist (e.g., domperidone), reported targets of the ergot alkaloids in cattle and horses, have had varying success (Oliver, 1997). Additionally, removal from toxic pasture 30 d before expected due date has had some success (Cross et al., 1995). However, there is an almost total lack of information concerning potential developmental toxicology (either in utero or postpartum) associated with the ergot alkaloids (i.e., presumed toxicants of E+ tall fescue) in grazers.

Respiration and Heart Rate

Respiration rates are reported as variable in the literature (Oliver, 1997). Two physiological effects of the alkaloids may account for the variability. First, decreased respiratory rates may be explained by actions of the alkaloids on the central nervous system. Alternatively, direct effects of the alkaloids on receptors in lung tissue and blood platelets may cause hypoxemia, resulting in a subsequent reflex increase in respiration rates. Which mechanism dominates is likely influenced by the environment surrounding the afflicted animal. Heart rate usually is unaffected or reflexively decreased in response to peripheral vasoconstriction and increased impedance to tissue blood flow (Oliver, 1997). Recent research by Aiken et al. (2007) supports the reflexive decrease (within 28 h) with a gradual increase back to baseline by 172 h after initial feeding of E+ tall fescue. These data, however, are in contrast to those in an earlier report by Walls and Jacobson (1970), where exposure of Holstein heifers to alcoholic extracts of toxic tall fescue (i.e., presumed to contain ergot alkaloid) resulted in elevated heart rates. Their earlier work (Carr and Jacobson, 1969) showed variable heart rate responses in male Holstein calves exposed to a similar alcoholic extract of toxic tall fescue. The variation in heart rate responses appears to be related to differences in dosage, routes of exposure, and/or nutrient status of the animals. Given that the ergot alkaloid levels are not known for the investigations conducted by Walls and Jacobson (1970) and Carr and Jacobson (1969), it is difficult to discern the exact relationship of their work to that of Aiken et al. (2007). These reports indicate a need for additional research to determine and understand how the ergot alkaloids affect heart and respiration rates.

Thermal Response, Heat Tolerance, and Stress

Hyperthermia is a primary characteristic of fescue toxicosis that often is used to define the magnitude of this condition. Environmental stress is a key determinant of the change in thermal status associated with fescue toxicosis (Hemken et al., 1984) and may result in increases or decreases in core body temperature from normal. In addition, there is a temporal determinant of the thermal stress–toxin response, with a distinct separation of short-term (acute) and long-term (chronic) responses that may encompass the adaptive response.

Initial studies in this area concentrated on the short-term response to an injected dose of readily available ergot alkaloids, such as ergotamine tartrate, known to reduce feed intake in domestic animals (Greatorex and Mantle, 1973, 1974; Osborn et al., 1992). Carr and Jacobson (1969) injected ergotamine tartrate (intramuscular, 35–92 μg/kg BW) into Holsteins at an 18.5°C T_{air} and noted an 8°C decrease in tail skin temperature, an indication of reduced blood flow. Administration (oral or intraperitoneal) of an 80% ethanol extract of E+ fescue under the same environmental condition also reduced skin temperature and increased rectal temperature. They suggested that reduced skin blood flow might diminish heat loss and result in hyperthermia during heat stress, with similar shifts in flow at cold air temperature to reduce skin temperature. Likewise, the reduced blood flow to appendages during cold stress could limit nutrient flow and result in tissue necrosis. Browning et al. (1998) also noted reduced skin temperature in Angus heifers injected at T_{air} = 35.2°C with either ergotamine tartrate or ergonovine maleate at rates of 5 to 7 mg/animal in both cases. Both treatments increased respiration rate (60–90 bpm); however, there was no significant effect on rectal temperature, suggesting that any increased heat was dissipated by increased heat loss. In contrast, intraperitoneal injection of heat-stressed cattle (T_{air} = 31°C) with ergovaline (5.2 μg/kg BW/d) for 3 d increased both core body temperature and respiration rate (Al-Haidary et al., 1995). Skin temperatures in the hip and back also were lowered, suggesting reduced blood flow and heat loss. These contrasting results indicated that ergovaline may be more potent than other ergopeptine alkaloids in producing signs associated with fescue toxicosis. McCollough et al. (1994) injected calves intravenously with ergotamine, ergine, and ergovaline and found that ergovaline was more effective than the other compounds in rate and magnitude of reduction in tail skin temperature, again supporting ergovaline as the more potent ergopeptine alkaloid.

The effect of ergopeptine alkaloids on thermoregulatory ability is highly dependent on T_{air}. This was demonstrated initially using classical biomedical animal models. In an early study, Roberts et al. (1949) injected rats intraperitoneally with ergotoxine (4.5 mg/kg BW) at T_{air} = 28 to 30°C. The rats were tested at ages 12 d (juvenile) and 37 d (adult) and exhibited hypothermic and hyperthermic responses, respectively. This differing response with age occurred as a result of the fact that this T_{air} was a cold stress for juveniles but a mild heat stress for the adults. It also demonstrated the dependency of the ergopeptine alkaloid response on T_{air}. Neal and Schmidt (1985) noted hypothermia in rats fed a diet with 50% E+ tall fescue for 15 d at T_{air} = 24 to 32°C and concluded that the rat is an inappropriate model for fescue toxicosis. However, they did not realize that the fescue toxicosis condition can shift core temperature above and below normal level at different T_{air} levels.

Few studies have been conducted under controlled environmental conditions to verify these shifts and determine mechanisms of action. Adult rats have been tested in environmental chambers at T_{air} values known to represent cold (7–9°C), thermoneutral (22°C), and hot (31–33°C) conditions following a single intraperitoneal injection of ergovaline (15μg/kg BW; Spiers et al., 1995; Zhang et al., 1994). Hyperthermia in the hot environment was preceded by a reduction in tail skin temperature with no shift in heat production, indicating that the cause was a reduction in cutaneous heat loss (Spiers et al., 1995). A decrease in core temperature occurred for the thermoneutral treatment; this is due to both an increase in peripheral heat loss, as indicated by an increase in tail skin temperature, and a reduction in heat production, as evidenced by reduced heat production (Zhang et al., 1994). Significant hypothermia also occurred in the cold after injection of ergovaline (Spiers et al., 1995), as a result of a reduction in heat production. It is apparent that ergovaline can affect either heat production or heat loss mechanisms, with the determining factor being which action is most in use at any given T_{air} (i.e., heat production in the cold and heat loss in the heat).

Most studies of the effect of fescue toxicosis on thermoregulation have been only a few hours or days, with few controlled long-term studies that would represent a more realistic scenario. Such studies are more complex than short-term ones because they must consider the time element and the possibility of adaptations to the test T_{air} and/or the toxins in question. Likewise, issues such as circadian rhythms and the indirect effect of reduced feed intake become critical. In general, there is a long-term reduction in feed intake of cattle grazing E+ tall fescue at T_{air} above 31°C (Hemken et al., 1981) and decreased ADG (Hoveland et al., 1983; Schmidt et al., 1982). The accompanying hyperthermia is due to a reduction in heat loss as a result of increased peripheral vasoconstriction (Osborn et al., 1992; Rhodes et al., 1991).

Both short- and long-term shifts in thermal status have been reported in animals administered E+ tall fescue under controlled environmental conditions. Al-Haidary et al. (2001) fed cattle a diet with E+ tall fescue seed (5 μg ergovaline/kg BW/d) for several days at 31°C. The primary effect on thermoregulatory ability (i.e., hyperthermia, increased respiration rate) was during the night, when there was a steady accumulation of metabolic heat following digestion of the daily meals, without the typical increase in the thermal gradient for heat dissipation (i.e., T_{air} was constant). As noted for rats, there was no change in metabolic rate or skin and respiratory vaporization rates. Skin temperature did not increase with core temperature, suggesting that there was little increase in peripheral heat loss under these conditions (Osborn et al., 1992; Rhodes et al., 1991; Solomons et al., 1989). Rhodes et al. (1991), using radiolabeled microspheres to measure vascular flow rates, found that flow rate to the skin covering the ribs was reduced in steers fed a diet containing E+ fescue seed (0.52 mg/kg ergovaline). Gadberry et al. (2003) noted that lambs fed a 10% E+ fescue seed diet (640 μg/kg) for 14 d during heat stress had reduced feed intake and ADG as well as evidence of reduced peripheral heat loss. No increase in the level of hyperthermia was noted to support a vasomotor response preceding the body temperature response. Aldrich et al. (1993a,b) fed steers an E+ tall fescue diet (285 μg/kg ergovaline) for 20 d at T_{air} = 32°C and noted hyperthermia with no effect on metabolic heat production or respiratory vaporization. However, skin vaporization was reduced by 50%; this observation was used to explain the hyperthermia. A rodent model for fescue toxicosis has been used to determine the long-term response of rats to fescue toxicosis (Spiers et al., 2005). Adult male rats, implanted intraperitoneally with temperature transmitters to monitor core temperature and general activity, were fed an E+ or an E− seed diet. Hypothermia was noted at thermoneutrality, with hyperthermia during heat stress, supporting observations in long-term studies in cattle. Activity level was lower in rats fed the E+ diet than in control rats during all periods. This response has not been measured in cattle or other species because similar transmitting sensors are unavailable for large animals.

Circadian shift in internal body temperature often has been overlooked in determining the change in thermal status associated with fescue toxicosis. The recent advent of thermal sensors now allows for this evaluation. In one study, beef calves were exposed to 31°C for 3 d and then fed a diet containing E+ tall fescue seed (5 μg ergovaline/kg BW/d) for 5 d while remaining at this T_{air} (Al-Haidary, 1995; Al-Haidary et al., 1995). The effects of this treatment were seen near midnight, with an increase in core temperature above control level. Likewise, there was an increase in respiration rate at this time. None of the other variables (i.e., skin temperature, skin or respiratory vaporization, metabolic rate) was affected. This would suggest that differences in heat production and water vaporization, at least during the daily peak in thermal status, are not responsible for noted shifts in body heat content associated with intake of E+ tall fescue. A more likely explanation would be the inability to increase peripheral blood flow to augment heat loss and dissipate the accumulated daily heat during the night.

Vascular Function

It is clear that fescue toxicosis results in major impacts on the cardiovascular system. These impacts include vasoconstriction, a thickened medial layer of blood vessels, endothelial cell damage, vascular stasis and thrombosis, ischemia, and finally gangrene (Thompson et al., 1950; Burfening, 1973; Culvenor, 1974; Garner and Cornell, 1978; Seawright, 1982; Coppock et al., 1989; Dyer, 1993; Oliver and Schultze, 1997; Shappell, 2003; Oliver, 1997, 2005; Klotz et al., 2007). The thickened medial layer of blood vessels in animals with fescue toxicosis has been linked to hyperplasia of the smooth muscle layer induced by ergot alkaloids, as reported by Strickland et al. (1996) using isolated vascular smooth muscle cells in vitro. Moreover, results of in vitro vascular bioassays (Solomons et al., 1989; Oliver et al., 1992, 1993, 1998; Klotz et al., 2006, 2007) have strongly suggested that the hyperthermia of fescue toxicosis is associated with the ergot alkaloids of E+ tall fescue. By inducing vasoconstriction as well as vascular smooth muscle cell hyperplasia (Oliver and Schultze, 1997) and endothelial cell damage, these alkaloids could reduce substantially blood flow to peripheral tissues, thereby reducing efficiency of heat transfer from core body tissue to the surface for dissipation. These postulations are substantiated as result of peripheral vasoconstriction being a measurable response to consumption of E+ tall fescue (Rhodes et al., 1991; Oliver et al., 1998). Additionally, Aiken et al. (2007) showed with Doppler ultrasonography that heifers consuming E+ tall fescue seed (0.85 and 0.36 μg/g dry matter for ergovaline and ergovalinine, respectively) had reduced caudal artery area and blood flow rates in comparison with baseline measures (i.e., animal as own control) as well as to measures in heifers receiving E– seed. However, it is currently unclear which ergot alkaloids, metabolites thereof, and/or alkaloid combinations found in E+ tall fescue are the primary toxicants or the combination of mechanisms by which these alkaloids may affect cardiovascular function.

Ergovaline has been reported as the most abundant of the ergopeptine alkaloids produced in E+ tall fescue (Yates et al., 1985; Lyons et al., 1986). This led to the early presumption that ergovaline was the primary toxicant in the fescue toxicosis syndrome. Much of the pharmacologic research concerning ergopeptines has been conducted using ergotamine, an ergopeptine chemically similar to ergovaline, but produced at much lower levels in E+ tall fescue (Yates et al., 1985). Ergotamine has been used primarily because of its broader availability as a result of its being used for treatment of migraines. Ergotamine has been shown to elicit contractile responses in bovine dorsal pedal vein (Solomons et al., 1989), cranial branch of the bovine lateral saphenous vein (Klotz et al., 2007), equine lateral saphenous vein and dorsal metatarsal artery (Abney et al., 1993), and rat tail artery (Schöning et al., 2001). Similarly, ergovaline has been shown to be a potent vasoconstrictor of bovine uterine and umbilical arteries (Dyer, 1993) and rat tail and guinea pig iliac arteries (Schöning et al., 2001), as well as most recently of the cranial branch of the bovine lateral saphenous vein (Klotz et al., 2006, 2007; Fig. 12–1A). Additional recent research by Klotz et al. (2006, 2007; Fig. 12–1C, 12–1D) clearly indicates that the ergopeptines, ergovaline and ergotamine, are more potent and efficacious vasoconstrictors than lysergic acid. In fact, lysergic acid

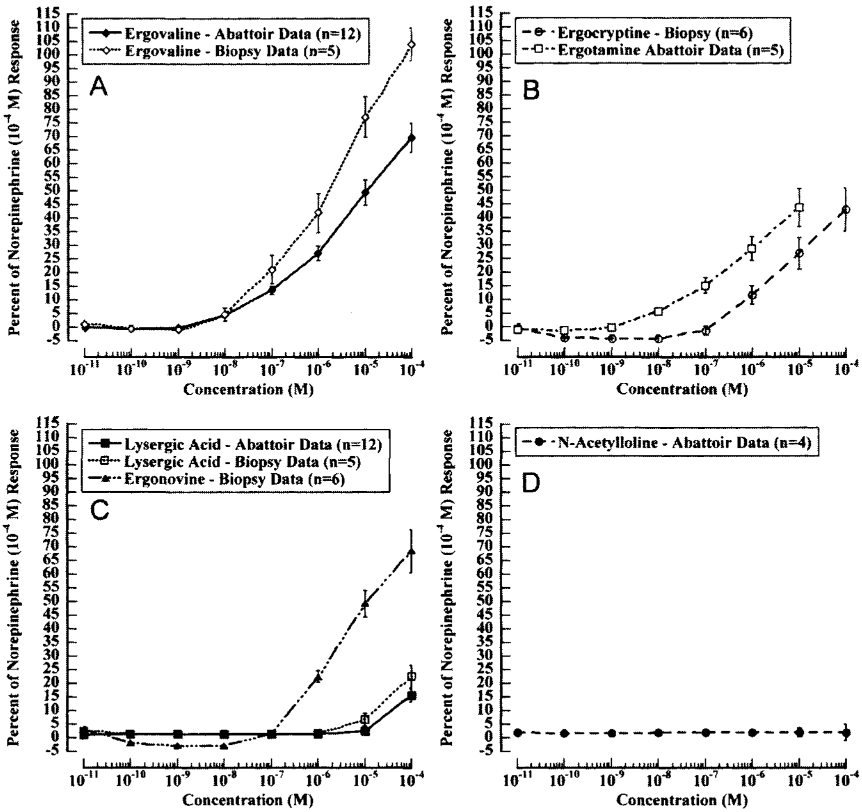

Fig. 12–1. Contractile response of the cranial branch of the bovine lateral saphenous vein in vitro to various alkaloid treatments. Data were compiled from several published (Klotz et al. 2006, 2007) and unpublished research trials (unpublished data, J.R. Strickland lab, 2007). (A) Contractile response of ergovaline in vessels collected from abattoir animals (Klotz et al., 2007) and surgical biopsy of naïve animals (Klotz et al., 2008). (B) Contractile response of ergocryptine in vessels from biopsy of naïve animals (Klotz et al., 2008) and ergotamine response in vessels collected from abattoir animals (Klotz et al., 2007). (C) Contractile response of lysergic acid, ergonovine, and ergocryptine in vessels from biopsy of naïve animals (Klotz et al., 2008) and lysergic acid in vessels collected from abattoir animals (Klotz et al., 2007). (D) Contractile response of *N*-acetylloline in vessels collected from abattoir animals (Klotz et al., 2008).

is at least 1000-fold less potent than ergovaline. Ergovaline begins its contractile response at the 10^{-8} M concentration and equals the contractile response of 10^{-4} M lysergic acid at a concentration of 10^{-7} M. Whereas the maximal contractile response of lysergic acid was 15 to 20% of the norepinephrine reference dose (10^{-4} M), that of ergovaline was 70 to 105% of the norepinephrine reference dose.

Prior exposure to ergot alkaloids (e.g., tissue from abattoir animals; Klotz et al., 2007, 2008; Fig. 12–1A, 12–1B) apparently attenuates the effect of these alkaloids on vasoconstriction in vitro when compared with animals with no prior exposure (i.e., naïve cattle). These observations support earlier findings by Oliver et al. (1998), in which a shift in α-2 adrenergic receptor activity was noted as being affected by prior exposure to E+ tall fescue (Fig. 12–2). Additional controlled studies are needed to confirm and define these apparent differences between cattle

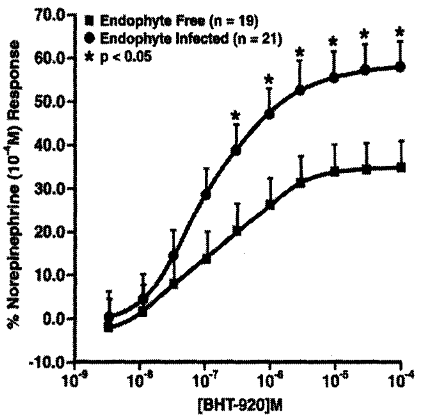

Fig. 12–2. Mean contractile dose response of lateral saphenous vein (cranial branch) of cattle in vitro to the selective α-2 adrenergic receptor agonist BHT-920. Cattle were pastured on E− (0%) or E+ (100%) (*N. coenophialum*) tall fescue for 55 to 85 d (mid March to mid June, 1993, 1994, and 1996). Treatments (E− and E+) were different (*P* < 0.05) (from Oliver et al., 1998).

consuming E+ and E− tall fescue. Klotz et al. (2008) also showed that apparently there was no synergistic, subtractive, or additive effects of ergovaline, lysergic acid, or *N*-acetylloline in mixtures on vasoactive potential of these alkaloids in this in vitro model. As expected, *N*-acetylloline showed no contractile effect in this system (Fig. 12–1D), providing evidence that the saturated pyrrolizidine alkaloid class of compounds may not be involved in fescue toxicosis. As the in vitro studies of Klotz et al. (2006, 2007) show, lysergic acid is at best a weak vascular toxicant in the periphery. As such, it is tempting to speculate that the primary toxicants associated with tall fescue will be those ergot alkaloids that are more structurally complicated, such as ergovaline.

Although the exact mechanism of alkaloid-induced vascular toxicity in ungulates is not completely clear, several lines of evidence implicate adrenergic and serotonergic receptor systems (Oliver, 1997, 2005). For example, pharmacologic treatments for reversal of severe vaso-spastic disease induced by ergot alkaloids typically have been most successful when α-adrenergic receptor antagonists have been used (Byrne-Quinn, 1964; Fedotin and Hartman, 1970; McLoughlin and Sanders, 1972; Greene et al., 1977; Larson et al., 1993). This would implicate the α-adrenergic receptors as good candidate targets for alkaloid interaction at the level of the blood vessel. In fact, Oliver et al. (1998) demonstrated clearly that segments of the cranial branch of the lateral saphenous vein from cattle consuming E+ tall fescue have increased contractile response to BHT-920, a selective α-2 adrenergic receptor agonist (Fig. 12–2), when compared with those from animals grazing E− tall fescue pasture. Oliver et al. (1993) also reported that the serotonin 5-HT_2 and α-1 adrenergic receptors were sites of interaction for the ergot alkaloid, lysergic acid, a relatively weak vascular contractor.

Biogenic Amine Receptor Interactions

In addition to those already mentioned, various other biogenic amine receptors are known to be affected by the ergot alkaloids of E+ tall fescue. For example, stimulation of α-2 adrenergic receptors by the alkaloids (Oliver et al., 1998) resulted in enhancement of blood platelet aggregation, which likely is involved in the coagulopathies and tissue necrosis (fescue foot) that occur with severe toxicity (Oliver, 1997, 2005). Stimulation of the dopamine-2 receptor (Larson et al., 1994, 1995) by ergot alkaloids found in E+ tall fescue is known to cause a decrease in prolactin secretion, which is linked to decreased milk secretion and agalactia in animals that graze E+ tall fescue (Strickland et al., 1993). Ergot alkaloids (i.e., ergine, ergovaline) also appear to interact with serotonin-2 receptors. Oliver and Abney (1989) and others (Dyer, 1993, 2000; Oliver et al., 1993; Vanhoutte and Luscher, 1986) have found that serotonin-induced contraction of vascular smooth muscle was associated with serotonergic-2 receptor activity. Serotonin is known to affect the hypothalamic satiety center, with increased levels resulting in suppression of appetite (Rossi-Fanelli and Cangiano, 1991), a possible mechanism by which ergot alkaloids might decrease feed intake. Support of alkaloid effects on neurotransmitter systems has been provided by Porter (1995) and Oliver et al. (2000b). Whereas Porter (1995) demonstrated that cattle grazing E+ tall fescue have increased serotonin metabolites in central nervous system tissues, Oliver et al. (2000b) showed increased tryptophan levels in sera of cattle grazing E+ tall fescue. This latter finding also is a condition that results in decreased feed intake (Smith, 1992; Porter, 1995; Meloche and Smith, 1995; Smith and Seddon, 1998).

Blood, Immunity, and Inflammation

Most blood cellular parameters are not affected by E+ tall fescue intake; however, E+ tall fescue increased the number of erythrocytes and decreased their size (mean corpuscular volume) and hemoglobin values (Table 12–1, Oliver et al., 2000a). Reduced Cu levels probably contribute to the decreased mean corpuscular volume and have decreased mean corpuscular hemoglobin values owing to inhibitory effects on hemoglobin synthesis. Enzymatic activity in general, and hepatic enzyme activity in particular, were decreased by intake of E+ tall fescue (Thompson and Stuedemann, 1993; Stuedemann and Thompson, 1993; Schultze et al., 1999; Oliver et al., 2000a). Many factors lower enzymatic activity, but decreased feed intake may be the factor most responsible (Oliver et al., 2000a), resulting in reduced growth and tissue metabolism and mass. Serum cholesterol levels were consistently lowered, as well as serum globulin levels (Table 12–2; Oliver et al., 2000a). Specifically, α and γ globulin levels were lowered (Table 12–3, Schultze et al., 1999).

Most mineral levels were unaffected by E+ tall fescue intake (Table 12–4, Oliver et al., 2000a). However, serum Cu levels were decreased (Saker et al., 1998; Oliver et al., 2000a). Dennis et al. (1998) documented lowered Cu levels in E+ tall fescue, which may account for the lowered serum Cu levels in cattle that graze E+ tall fescue. Vaccination response was similar in cattle that grazed E− or E+ tall fescue (Rice et al., 1997). However, in a later study, E+ tall fescue exposure lowered immune function in steers, which was associated with Cu deficiency (Saker et al., 1998). In addition, as noted earlier, γ globulin levels are consistently suppressed by exposure to E+ tall fescue (Table 12–3, Schultze and Oliver, 1999). Thus, some compromise in immune status apparently occurs in animals that consume E+ tall fescue. The degree to which this results in morbidity or mortality has yet to be determined.

The vascular endothelium has been described as the cellular target for initial injury by the ergot alkaloids (Thompson et al., 1950). Direct evidence of endothelial damage by ergot alkaloids has been provided recently by exposing isolated bovine endothelial cells to ergovaline and ergine in vitro (Shappell, 2003). The ergine treatment at 10^{-5} M concentration had minimal effect, while ergovaline at this dose gave cytotoxic effects. At 10^{-4} M concentration, ergovaline caused

Table 12–1. Hemogram values for steers grazing endophyte free and endophyte infected tall fescues.†

Item	E− tall fescue (n = 8)	E+ tall fescue (n = 8)	$P > F$	Reference range‡
Red blood cells, 1 × $10^6/\mu L$	8.33 ± 0.15	8.83 ± 0.15*	0.150	5–10
Hemoglobin, g/dL	12.50 ± 0.17	12.60 ± 0.17	0.747	8–15
Hematocrit, %	34.40 ± 0.48	34.80 ± 0.48	0.487	24–46
Mean corpuscular volume, fL	41.40 ± 0.46	39.50 ± 0.46**	0.004	40–60
Mean corpuscular hemoglobin, pg	15.10 ± 0.18	14.30 ± 0.18**	0.002	11–17
Mean corpuscular hemoglobin concentration, g/dL	36.40 ± 0.20	36.20 ± 0.20	0.385	30–36
Platelets, 1 × $10^3/\mu L$	573.00 ± 37.00	586.00 ± 0.37	0.783	100–800
Mean platelet volume, fL	7.70 ± 0.33	7.10 ± 0.36	0.217	3.5–6.5
White blood cells, 1 × $10^3/\mu L$	7.57 ± 0.29	8.20 ± 0.29	0.109	4–12
Neutrophils, 1 × $10^3/\mu L$	2.44 ± 0.21	2.45 ± 0.21	0.992	0.6–4
Lymphocytes, 1 × $10^3/\mu L$	6.55 ± 0.16	6.66 ± 0.16	0.658	2.5–7.5
Monocytes, 1 × $10^3/\mu L$	0.33 ± 0.03	0.36 ± 0.03	0.338	<0.0–0.9
Eosinophils, 1 × $10^3/\mu L$	0.68 ± 0.06	0.48 ± 0.06*	0.024	<0.0–2.4
Basophils, 1 × $10^3/\mu L$	0.001 ± 0.001	0.002 ± 0.001	0.676	<0.0–0.2

* $P < .05$.; ** $P < .01$. From Oliver et al. (2000a).

† Repeated measures ANOVA. Twenty different bleed dates, April–August 1996 to 1998. Least square means (±SEM).

‡ Taken from Duncan et al. (1994) and Clinical Chemistry Service, College of Veterinary Medicine, University of Tennessee.

Table 12–2. Mean value of serum analytes for steers grazing endophyte free and endophyte infected tall fescues.†

Item	E− tall fescue (n = 8)	E+ tall fescue (n = 8)	$P > F$	Reference range‡
Albumin, g/100 mL	3.58 ± 0.05	3.71 ± 0.05	0.051	3.0–3.55
Albumin/globulin ratio	1.10 ± 0.04	1.32 ± 0.04***	0.001	0.84–0.94
Alkaline phosphatase, U/L	84.4 ± 5.6	76.6 ± 5.6	0.330	0.01–488
Alanine aminotransferase, U/L	37.8 ± 1.8	31.3 ± 1.8**	0.010	11–40
Aspartate aminotransferase, U/L	86.3 ± 4.9	75.3 ± 4.7	0.110	78–132
Cholesterol, mg/100 mL	107.0 ± 4.2	91 ± 4.2**	0.006	80–120
Creatinine, mg/100 mL	1.38 ± 0.04	1.58 ± 0.04***	0.001	1.0–2.0
Estradiol, pg/mL§	7.25 ± 0.71	6.59 ± 0.56	–	–
Gamma glutamyl transferase, U/L	12.9 ± 0.6	13.2 ± 0.6	0.711	6.1–17.4
Globulin, g/100 mL	3.37 ± 0.07	2.97 ± 0.07***	0.001	3.0–3.48
Glucose, mg/100 mL	79 ± 4.9	72 ± 4.9	0.277	45–75
Lactic dehydrogenase, U/L	926 ± 29	860 ± 28	0.103	692–1445
Prolactin, ng/mL	214 ± 57	13.2 ± 57*	0.012	–
Total bilirubin, mg/100 mL	1.63 ± .04	1.74 ± 0.04*	0.042	0.01–0.5
Total protein, g/100 mL	6.93 ± .09	6.68 ± 0.08*	0.037	6.74–7.46
Urea N, mg/100 mL	16.1 ± 0.42	16.2 ± 0.41	0.898	20–30

* $P < .05$; ** $P < .01$; *** $P < .001$. From Oliver et al. (2000a).

† Repeated measures ANOVA. Twenty different bleed dates, April–Aug. 1996 to 1998. Least square means (±SEM).

‡ Taken from Kaneko et al. (1997) and Clinical Chemistry Service, College of Veterinary Medicine, University of Tennessee.

§ Estradiol values were determined only in 1998 (49 samples from steers grazing E− tall fescue and 52 samples from steers grazing E+ tall fescue).

Table 12–3. Globulin electrophoresis from the serum of cattle grazing endophyte free and endophyte infected tall fescues.†

Tall fescue	Alpha globulins	Beta globulins	Gamma globulins
	g/dL		
E−	1.57 ± 0.05	0.83 ± 0.04	2.30 ± 0.14
E+	1.32 ± 0.01*	0.95 ± 0.11	1.40 ± 0.51*

* Significantly different from control ($p < 0.05$). From Schultze et al. (1999).

† Data are presented as mean ± standard error. $N = 3$/group.

Table 12–4. Mean values of serum minerals for steers grazing endophyte free and endophyte infected tall fescues.†

Item	E− tall fescue ($n = 8$)	E+ tall fescue ($n = 8$)	$P > F$	Reference range‡
	mg/kg			
Ca	100.3 ± 0.9	97.3 ± 0.8	0.133	80–114
Cu	0.72 ± 0.02	0.62 ± 0.02	0.003**	0.72 ± 0.02§
Fe	1.46 ± .06	1.50 ± 0.06	0.664	0.57–1.62
Mg	20.0 ± 0.4	19.8 ± 0.4	0.400	15–29
P (total)	130.9 ± 2.5	127.3 ± 2.4	0.355	45–60¶
K	181.9 ± 2.6	184.8 ± 2.4	0.218	140.8–191.6
Na	3492 ± 20	3460 ± 18	0.380	3126–3310
Zn	0.74 ± 0.03	0.71 ± 0.02	0.448	0.68 ± 0.23#

** $P < .01$. From: Oliver et al. (2000a).

† Repeated measures ANOVA. Fourteen different bleed dates, April to August 1998 and 1999. Least square means (±SEM).

‡ Taken from Duncan et al. (1994).

§ Taken from Saker et al. (1998).

¶ Taken from Puls (1994). Reference range is for inorganic P levels only, which average about 40% of total P levels.

Taken from Underwood (1977).

marked cytotoxicity, while ergine caused only a slight toxic effect. Thus, the presence of ergot alkaloid–induced toxicity to endothelial cells in vivo (possibly as ergovaline effect alone or maybe as a synergistic response with other alkaloids present in E+ tall fescue) would result in elaboration of inflammatory mediators, as well as change in the clotting factor profile of the animal. Strickland et al. (1996) demonstrated a mitogenic effect of alkaloids (ergonovine, α-ergocryptine, ergovaline, *N*-acetyl loline) on isolated bovine vascular smooth muscle cells from the dorsal metatarsal artery, indicating that these alkaloids have an effect on blood vessel reactivity in cattle and that synergistic action of the alkaloids may be possible (Williams et al., 1975). Furthermore, damaged endothelial cells would allow access of various mediator agents to the underlying smooth muscle cell layer of blood vessels (Quinones-Baldrich, 1993), contributing to the thickened vessels seen at necropsy (Oliver and Schultze, 1997).

The pathological changes that occur from ergot alkaloid exposure in tall fescue toxicosis have inflammation as an important etiologic factor. Systemic inflammatory response syndrome, a condition whereby several bioactive compounds have been released from the cardiovascular tissues in response to a pathological insult, can be linked to many of the clinical signs of tall fescue toxicosis. These include: febrile response, hyperalgesia and lameness, stasis of blood in peripheral vessels, and coagulation defects. Biologically active substances produced by endothelial cells in the sera of cattle are impacted by exposure to ergot alkaloids and include increased angiotensin converting enzyme activity (unpublished data, J.W. Oliver, 1998) leading to increased angiotensin II levels. Angiotensin II is a potent vasoconstrictor substance that also impacts fluid and electrolyte balance through release of antidiuretic hormone and aldosterone (Drouet et al., 1988). In addition, activation of angiotensin II receptors on smooth muscle cells is known to induce mitogenesis (Quinones-Baldrich, 1993). There also is a trend for increased von Willibrand Factor (vWF) levels in cattle exposed to E+ tall fescue (unpublished data, J.W. Oliver, 1998). The vWF is a factor that functions as an adhesion molecule in the subendothelium for blood platelets during vascular injury (Ware and Heistad, 1993). Increased vWF levels are associated with increased risk for hypercoagulability and thrombosis, events prominent in severe tall fescue toxicosis. Additionally, thromboxane A_2 (TXA_2) levels are increased in cattle that graze E+ tall fescue (unpublished data, J.W. Oliver, 1998). Thromboxane A_2 is a potent vasoconstrictor substance that is formed in blood platelets; increased blood levels of TXA_2 indicate that thrombotic events are occurring. Thromboxane A_2 also is known to have broncho-constrictive effects (Campbell, 1990). Nitric oxide, a potent vasorelaxant produced by vascular endothelium in the periphery (Chung and Fung, 1990; Gerstberger, 1999; Yamashita et al., 1998; Mills et al., 1997) also could be involved in alkaloid-induced perturbations of vascular function. In support of this supposition, Al-Tamimi et al. (2007) noted that rats fed a wild-type E+ tall fescue diet had lower blood nitric oxide level than controls and that the nighttime hyperthermia associated with fescue toxicosis was reduced by administration of molsidomine, a nitric oxide donor, suggesting the role of nitric oxide in generating this response. In addition, Oliver et al. (2000b) showed that arginine levels are decreased in cattle that graze E+ fescue, potentially resulting in nitric oxide deficiency. In fact, Oliver et al. (2001a,b) noted that nitric oxide synthesis was decreased in animals grazing E+ tall fescue (Oliver et al., 2001a,b), contributing to vasoconstriction and coagulopathy conditions.

Future Research Directions

The development and use of new vascular bioassays based on vasculature from disparate regions in the bodies of the animals (e.g., core vs. peripheral tissue) as well as bioassays for other physiological systems are needed to delineate fully the alkaloids responsible for the complete fescue toxicosis syndrome and the mechanisms of intoxication. Accurate, sensitive, and logistically favorable analytical protocols are needed to track the alkaloids and their metabolism throughout the body to understand the toxicokinetics and dynamics of the toxicants to the animal. Only recently have researchers begun to use genomic, proteomic, and metabolomic tools to study the effects of tall fescue toxicants on cellular/organismal function and performance (Bhusari et al., 2006; Settivari et al., 2006; Jones et al., 2004). The increased application of these tools to the problem of tall fescue toxicosis offers opportunities to elucidate more completely the molecular consequences of intoxication and subsequently will aid in the selection of prophylactic and treatment protocols for the disease.

Plane of nutrition and/or toxicants found in E+ tall fescue could affect microbial activity in both the rumen and the cecum, thereby potentially moderating the effects of the toxicants on digestion. Direct alterations of ruminal function resulting from tall fescue ingestion have been demonstrated, but not directly linked to the endophyte. Therefore, it is critical that additional research be conducted concerning not only the effects of the alkaloids on rumen function but of the plane of nutrition on the metabolism of the compounds. Evaluation tools such as Doppler ultrasound imaging are needed that provide immediate measures of basic physiological functions as affected by the consumption of E+ tall fescue. These tools would help validate the in vitro bioassays and cell culture methods being used to dissect the mechanisms of action.

Conclusions

The pathogenesis of tall fescue toxicosis in animals is due in part to effects of alkaloids, among which ergovaline is prominent, on the cardiovascular system. The effects include thickened blood vessels, increased vascular tone, hypercoagulability and sludging of blood, and, depending on severity, ischemia and gangrenous necrosis of tissues. The ischemic response of blood vessels in the skin and lungs contributes to heat stress problems and also likely influences reproductive performance and nutrient flux in the gastrointestinal system. The well-known effect of alkaloids on reducing feed intake may have an associated effect on important nutrient factors. In support of this supposition, a trend has been demonstrated for increased tryptophan levels to occur in the blood of cattle that had grazed E+ tall fescue. This increase may have an impact on serotonin levels in the hypothalamus and subsequently may affect feeding behavior. Similarly, a suppressive effect of E+ tall fescue intake on serum arginine levels has been demonstrated. The decrease in serum arginine has been linked to decreased nitric oxide availability that may ultimately enhance vasoconstrictive and hypercoagulability effects. All these biological effects have the potential to affect efficiency of production. This lost efficiency results in increased production costs, which ultimately diminish sustainability of forage-animal production. This problem likely will be solved by a variety of treatments and management protocols aimed at improving animal tolerance or limiting exposure to E+ tall fescue. Both approaches require more fundamental biological information concerning the exact causative agents and the mechanisms involved.

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